REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

As correctly indicated in the Office Action Summary, claims 1-61 are pending in the application. Claims 3-5 and 8-47 have been withdrawn from consideration. Claims 1, 2, 6, 7 and 48-61 stand rejected.

Claim 6 has been amended to more clearly recite the claimed subject matter by indicating which recited sequences are considered as a group. The scope of claim 6 has not been altered. Support for claim 6 as amended is as previously described. No prohibited new matter has been introduced by way of the instant amendment. Applicants reserve the right to file a continuation or divisional application on the canceled subject matter.

Regarding the sequence listing:

The Examiner has objected to the application and sequence listing as failing to comply with the requirements of 37 C.F.R. §§ 1.821- 1.825. Sequences that were disclosed in the specification, but were not designated with appropriate sequence identifiers have been identified. By this amendment, the specification is amended to insert appropriate sequence identifiers. Further, a substitute sequence listing is submitted herewith, which includes sequences that were inadvertently omitted from the previously filed sequence listing. It is believed that the application is now in compliance with 37

C.F.R. §§ 1.821- 1.825. Accordingly, withdrawal of the objection is respectfully requested.

Previous rejections:

The rejection of claims 6 and 7 under 35 U.S.C. § 112, second paragraph, the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, and the rejection of claims 1 and 2 under 35 U.S.C. § 103, that were set forth in Paper No.17 have not been reiterated in the present Office Action (Paper No. 21). Therefore, in accordance with numbered paragraphs 2 and 14-16 of Paper No. 21, Applicants understand that these rejections have been obviated by the amendments to the claims and/or Applicants' arguments submitted in the Reply dated February 3, 2003 (Paper No. 20).

Claim rejections under 35 U.S.C. §§ 101 and 112, first paragraph:

Claims 1, 2, 6, 7 and 42-61 have been rejected under 35 U.S.C. §§ 101 and 112, first paragraph. It is noted that claims 42-47 are among the claims that have been indicated as withdrawn from consideration. With regard to 35 U.S.C. § 101, it is alleged in the Office Action that the rejected claims are not supported by either a substantial asserted utility or a well established utility. With regard to 35 U.S.C. § 112, first paragraph, it is further alleged that if the claims are not supported by either a substantial asserted or a well established utility, one skilled in the art would not know how to use the claimed invention. The rejections are respectfully traversed.

As noted in numbered section 9 on page 4 of the Office Action, the rejected claims are directed to methods of identifying a molecule involved in lipid regulation. There is no

allegation that the identification of a molecule involved in lipid regulation is not a specific and substantial utility. Rather, at page 7, the alleged basis of the rejection is set forth as "[T]he specification fails to disclose the direct involvement of either HBM or Zmax1 in lipid regulation." Thus, the rejection appears to be directed at the credibility of the asserted utility.

However, contrary to the allegations in the Office Action, the involvement of HBM and Zmax1 in lipid regulation is clearly disclosed in the application. *See* entire specification, *e.g.*, at pages 10-11. Furthermore, the credibility of the asserted utility is supported by scientific data disclosed in the specification. *See, e.g.*, specification Example 3 at pages 125-128.

The data regarding lipid regulation disclosed in the specification must be evaluated in the context of the other teachings of the specification. Thus, Applicants note the following by way of background. The Zmax1 and HBM proteins are related; HBM is a polymorphic variant of Zmax1. HBM has a glycine to valine change at residue 171 of Zmax1. *See* specification at pages 18-19. As disclosed in the specification, a patient having significantly elevated bone mass was identified. *See, e.g.*, Example 1 at pages 123-4. Subsequently, members of the patient's kindred were tested for bone mass density and genotyped to identify the genomic region associated with the high bone mass trait. *See, e.g.*, specification at pages 28-74. The HBM phenotype was defined by those individuals having a statistically significant Z-score of a measure of bone mass density. *Id.* Through extensive experimentation, it was discovered that members of the kindred that have the HBM variant of Zmax1 display the high bone mass phenotype. *See, e.g.*, specification at page 74. Thus, it has been established that a single altered amino acid of Zmax1 is

sufficient to confer a phenotypic change in bone mass density. Thereby, it has been further established by the Applicants that Zmax1 is involved in the regulation of bone mass density and that the HBM polymorphism of Zmax1 is responsible for the HBM phenotype.

The credibility of the asserted utility is supported by experimental data.

As with the determination of the cause of the high bone mass phenotype, experiments were conducted on samples obtained from members of the same kindred to determine whether Zmax1 and HBM were involved in lipid regulation. These experiments are disclosed and analyzed in Example 3 of the specification at pages 125 to 128. Standard diagnostic protocols were used. The actual data is presented in the table at page 128 of the specification. At least the following was determined from this data: that affected members (*i.e.* members having the HBM polymorphism of Zmax1) ***had statistically significant reductions in triglyceride levels, and lower VLDL levels.*** *See* specification at page 127. At a high level of confidence ($p=0.06$), it was also found that males having the HBM polymorphism had higher HDL levels, with the ratio of LDL to HDL being significantly different. *Id.* Thus, the data disclosed in the specification clearly establish that the HBM polymorphism of Zmax1 is associated with an altered lipid profile in addition to its role in bone mass modulation. Further, in the same manner that it was determined that Zmax1 and the HBM variant thereof are involved in bone mass regulation, it has also been established that Zmax1 and the HBM variant thereof are involved in lipid regulation.

The credibility of the asserted utility is consistent with knowledge in the art.

The data disclosed in the specification is consistent with the knowledge in the art at the time the application was filed. For example, the Zmax1 protein has a degree of sequence homology and features in common with the LDL receptor. *See*, specification at

pages 83-84. While the noted relationship between Zmax1 and the LDL receptor, standing alone, would not be sufficient to establish whether Zmax1 is involved in lipid regulation, this observation supports the credibility of the conclusions indicated by the experimental results.

In addition, Zmax1 binds to several proteins including apolipoprotein E (Apo E). *See* specification at page 115. The role of Apo E in lipid regulation was well established at the time. Thus, the data disclosed in the specification is consistent with observed protein binding interactions of Zmax1. Furthermore, the English language abstract of Zabaglia *et al.*, *Cad Saude Publica*, 14:779-85, 1998 (attached as Exhibit A), shows correlations between certain lipid profile parameters and bone mineral density. Zabaglia *et al.* reports that in postmenopausal women, HDL levels showed an inverse correlation to bone mass to a very high degree of statistical significance ($p=0.001$). High total cholesterol had a positive association with bone mineral density ($p=0.026$), and the LDL:HDL ratio showed a negative association with bone mineral density($p=0.002$). These results are consistent with a relationship between a lipid profile regulatory mechanism and a bone mass regulation pathway, such that a change can affect both lipid regulation and bone mass and the relationship between these parameters.

It is recognized that Zabaglia et al. concluded that lipid profile parameters are generally not useful as a diagnostic indicator of bone mass. This conclusion does not contradict the data disclosed in the present application. As can be seen from the table on page 128 of the specification, the Z-score of bone mass varied within the unaffected group (*i.e.* normal persons). Likewise, the lipid profile parameters varied within the unaffected group. However, when the mean parameter values of the affected and unaffected groups

are compared, the relationship becomes clear. Thus, although a lipid profile parameter may not be a precise predictor of bone mass, the correlations between parameters are significant support for the involvement of Zmax1 and HBM in lipid regulation discovered by the Applicants.

Independent reports confirm the asserted utility.

Further, the credibility of the asserted utility has been borne out in reports in the literature. For example, Parhami *et al.*, *J. Bone & Min. Res.*, 1:182-8, 2001 (Attached as Exhibit B) surveyed the history of the links between lipid regulation and bone mineral density in the introduction. Parhami *et al.* cites publications from long before the filing date of the present application (*i.e.* 1972 and 1992) as demonstrating that osteoperosis and cardiovascular disease are linked regardless of age. See Parhami *et al.* at first sentence. Publications from 1991, 1993 and 1999 are cited to show that low bone mineral density is associated with cardiovascular disease mortality. The credibility of the asserted utility is further confirmed by recent studies. For example, Fujino *et al.*, PNAS USA, 100:229-234, 2003 (Attached as Exhibit C) and Magoori *et al.*, *J. Biol. Chem.*, Manuscript M211987200, published online on December 31, 2002 (Attached as Exhibit D), have shown that Zmax1 (now called LRP5) is essential for normal cholesterol metabolism.

The Office Action does not provide a reason to doubt the asserted utility.

Despite the data presented in the specification, the allegation in the Office Action is that "[t]he only link between HBM and lipid regulation is the indication that persons with the HBM polymorphism show a generally lower serum level of triglycerides and VLDL and a generally higher serum level of HDL, compared to controls." Applicants submit that the disclosure of such *in vivo* data is more than sufficient to credibly establish the

involvement of HBM in lipid regulation. Further, despite the clear relationship between Zmax1 and HBM (differing at a single critical site), the Office Action alleges the "the only link between Zmax1 and lipid regulation is sequence homology between Zmax1 and the LDL receptor." However, the experimental data is equally relevant to the role of wild-type Zmax1, as well as the HBM polymorphism in lipid regulation. Applicants respectfully submit that, since it is the difference between the presence or absence of the HBM variant of Zmax1 that has been shown to correspond to an altered lipid profile by the *in vivo* data presented in the application, the link between Zmax1 and lipid regulation has thereby also been credibly established.

The cited references do not provide a reason to doubt the asserted utility.

The references cited in the Official Action in support of the present rejection do not provide a reason to doubt the credibility of the asserted utility. For example, Ye *et al.*, *Am. J. Clin. Nutr.*, 72:1275S-1284S, 2000 teaches that genes influence quantitative variations in plasma lipoprotein concentrations. Ye *et al.* reviews a series of polymorphisms in various genes involved in lipid regulation. In the section cited on page 6 of the Official Action ,Ye *et al.* reports that studies of the effects of dietary cholesterol have not been consistent as a result of a series of confounding factors. This means that it remains to be determined under what circumstances and for which polymorphisms a dietary intervention is indicated. However, this does not in any way cast doubt on whether those polymorphisms, or instant polymorphism, appear in genes related to lipid regulation. It certainly does not provide a reason to doubt the utility of the present invention. The question of whether a dietary change can affect lipid profiles simply has no bearing on the question of whether identifying a molecule that binds to a protein involved in lipid

regulation (such as HBM or Zmax1) has credible utility as a method for identifying a molecule that is involved in lipid regulation.

Willnow *et al.*, *Nature Cell Biol.*, 1:E157-E162, 1999 is also cited in support of this rejection on page 6 of the Official Action. Willnow *et al.* teaches that members of the LDL receptor family of proteins have many varied functions. This publication provides no reason to doubt the credibility of the asserted utility of the presently claimed invention, which is supported by *in vivo* data.

Identification of molecules that bind to a protein involved in lipid regulation is a well established utility .

Moreover, when the involvement of a protein on regulation of an important metabolic parameter has been identified, the utility of screening for other molecules that bind to or inhibit binding to that molecule has been well established. For example, Jin *et al.*, *Trends Endrocrin. & Metab.*, 13:174-8, 2002 reviews the state of the art in lipases. For example, Jin *et al.* cites publications from 1994-1999 reporting that a single nucleotide polymorphism in HL has been associated with increased levels of HDL-C. See, Jin *et al.* at 175, second column. Jin et al. concludes the review of lipases stating:

> "Because of their intimate relationship with HDL metabolism and function, they are likely to have important effects of atherosclerosis in humans. Indeed, several of these lipases are viable targets for new drug development." *Id.* at 177.

As described in the specification, for example at pages 115-117, the identification of molecules that bind to HBM and Zmax1, such as proteins, can be used to identify

molecules that are involved in lipid regulation. Further, as described, the actual observation of binding can be performed by any method recognized in the art. *Id.*

The requirements of both 35 U.S.C. §§ 101 and 112, first paragraph have been met.

With regard to the rejection under 35 U.S.C. § 112, first paragraph, it is alleged that "without a clear indication of the function of HBM and Zmax1, particularly with respect to lipid regulation, one of skill in the art would still have to perform an undue amount of additional[] experimentation in order to use HBM or Zmax1 as claimed." The reason that is alleged for holding that additional experimentation would be undue is that "involvement of HBM and Zmax1 in lipid regulation would have to be established before one could attempt to practice the claimed invention." Applicants respectfully submit that the involvement of HBM and Zmax1 in lipid regulation has been credibly established by the data disclosed in the specification considered in view of knowledge in the art at the time the application was filed, and has been confirmed by separate independent studies, as set forth above.

For at least the foregoing reasons, it is clear that the present application satisfies the requirements of 35 U.S.C. §§ 101 and 112, first paragraph in that a credible, specific and substantial utility for the claimed invention is described in the specification and supported by the disclosure of *in vivo* data consistent with the knowledge in the art at the time the application was filed. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 6, 7 and 42-61 under 35 U.S.C. §§ 101 and 112, first paragraph.

Claim rejection under 35 U.S.C. § 112, first paragraph:

Claims 6 and 7 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification. In particular, the amendment of claim 6 to recite "a Zmax1 nucleic acid comprising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G)" is objected to.

It is alleged that the specification does not explicitly disclose this negative limitation. Claim 6 is directed to identifying a molecule involved in lipid regulation by identifying a molecule that has a differential interaction with a HBM sequence versus a Zmax1 sequence. However, the polymorphism of Table 4 having the C/A base change at location 21119 (308G) corresponds to the HBM polymorphism, while the other polymorphisms of Table 4 do not appear to cause the HBM phenotype and therefore correspond to non-HBM variants of Zmax1. *See* specification at page 73. Thus, this negative limitation is necessarily implicated wherever a comparison between Zmax1 and HBM is described, for example in Claim 6 as originally filed. In view of the foregoing, withdrawal of the rejection of claims 6 and 7 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Claim rejection under 35 U.S.C. § 112, second paragraph:

Claims 6 and 7 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, it is alleged that there are two possible meanings of claim 6 depending on how the recited sequences are considered grouped. Without acceding to the Examiner's reasons, because Applicants believe that one of skill in the art would understand claim 6 as previously presented, claim 6 has been amended to insert grouping identifiers, (i) and (ii), and to replace the word "or" in step C with the word "versus" to more clearly

indicate the recited comparison. The scope of claim 6 has not changed. In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claims 6 and 7 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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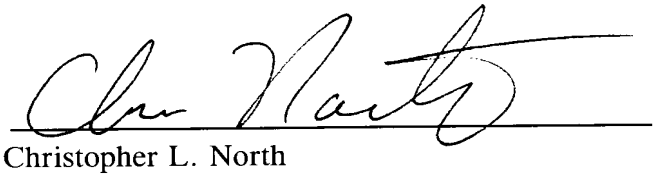
By: 

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